120

AF/1652

Practitioner's Docket No. 46906-2 DIV

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: S. Chatterjee

Serial No.: 09/282,879 Group No.: 1652

Filed: March 31, 1999 Examiner: Manjunath N. Rao

For: RECOMBINANT N-SMASEs AND NUCLEIC ACIDS ENCODING SAME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF
(PATENT APPLICATION--37 C.F.R. SECTION 1.192)

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on 29 May 2003.

NOTE: "Appellant must, within two months from the date of the notice of appeal under section 1.191 or within the time allowed for reply to the action from which the appeal was taken, if such time is later, file a brief in triplicate....." 37 C.F.R. Section 1.192(a) (emphasis added)

2. STATUS OF APPLICANT

This application is on behalf of

[ ] other than a small entity.
[X] a small entity.

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. SECTION 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

[X] deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

FACSIMILE

[ ] transmitted by facsimile to the Patent and Trademark Office (703) ___-____.

Signature

Date: December 1, 2003

Peter F. Corless
(type or print name of person certifying)

A statement:
[ ] is attached.
[X] was already filed.

3. FEE FOR FILING APPEAL BRIEF

Pursuant to 37 C.F.R. Section 1.17(c), the fee for filing the Appeal Brief is:

[X] small entity	$165.00
[ ] other than a small entity	$330.00

Appeal Brief fee due $ 165.00

4. EXTENSION OF TERM

NOTE: The time periods set forth in 37 C.F.R. 1.192(a) are subject to the provision of Section 1.136 for patent applications. 37 C.F.R. 1.191(d). See also Notice of November 5, 1985 (1060 O.G. 27).

NOTE: As the two-month period set in Section 1.192(a) for filing an appeal brief is not subject to the six-month maximum period specified in 35 U.S.C. 133, the period for filing an appeal brief may be extended up to seven months. 62 Fed. Reg. 53,131, at 53,156; 1203 O.G. 63 at 84. Oct. 10, 1997.

The proceedings herein are for a patent application and the provisions of 37 C.F.R. Section 1.136 apply.

(complete (a) or (b), as applicable)

(a) [X] Applicant petitions for an extension of time under 37 C.F.R. Section 1.136 (fees: 37 C.F.R. Section 1.17(a)(1)-(5)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
[ ]	one month	$110.00	$55.00
[ ]	two months	$420.00	$210.00
[ ]	three months	$950.00	$475.00
[X]	four months	$1,480.00	$740.00

Fee: $ 740.00

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

[ ] An extension for _____ months has already been secured, and the fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $ 740.00

or

(b) [ ] Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

5. TOTAL FEE DUE

The total fee due is:

Appeal brief fee	$ 165.00
Extension fee (if any)	$ 740.00

TOTAL FEE DUE $ 905.00

6. FEE PAYMENT

[X] Attached is a check in the sum of $ 905.00.
[ ] Charge Account No. _____ the sum of $ _____.

A duplicate of this transmittal is attached.

7. FEE DEFICIENCY

NOTE: If there is a fee deficiency and there is no authorization to charge an account additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in resuming the papers to the PTO Finance Branch in order to apply these charges prior to action on the cases. Authorization to change the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, 1065 O.G 31-33.

[X] If any additional extension and/or fee is required, this is a request therefor and to charge Account No. 04-1105.

AND/OR

[X] If any additional fee for claims is required, charge Account No. 04-1105.

Date: _____

Reg. No. 33,860

Tel. No.: 617-439-4444

SIGNATURE OF PRACTITIONER

Peter F. Corless
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Docket No. 46906

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: S. Chatterjee

SERIAL NO.: 09/282,879 GROUP: 1652

FILED: March 31, 1999 EXAMINER: M. Rao

FOR: RECOMBINANT N-SMASES AND NUCLEIC ACIDS ENCODING SAME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Applicant respectfully appeals the decision of the Examiner, dated November 27, 2002, finally rejecting claims 13-17 and 31.

This brief is being filed in triplicate. The requisite fee for filing this brief is enclosed herewith.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the Johns Hopkins University of Baltimore, Maryland, the assignee of the application.

II. RELATED APPEALS AND INTERFERENCES

To the knowledge of the undersigned, there are no current appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 1-31 have been presented in this application.

Claims 1-12 and 18-30 were subject to restriction and therefore cancelled without prejudice. The subject matter of claims 1-12 has been issued in parent case U.S. Patent 5,919,687, copy attached.

Claims 13-17 and 31 have been finally rejected and presently are on appeal (see the attached Appendix).

IV. STATUS OF AMENDMENTS (AFTER FINAL REJECTION)

No Amendments After Final Rejection were filed.

V. SUMMARY OF THE INVENTION

Appellant's claimed invention is directed to methods for identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder.

Methods of the invention in general comprise contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 and analyzing that mixture.

Appellant's independent claim 13 (the only pending independent claim) is representative of the subject matter on appeal and reads as follows:

Claim 13. A method for identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder, comprising

contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof,

wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent, wherein the fragment or derivative of the human neutral sphingomyelinase has at least about 50% of the activity of the protein of SEQ ID No. 2.

SEQ ID. No. 2 is defined in the application as filed. The terms "fragment" and "derivative" as set forth in claim 13 are defined at page 8, lines 16-23 of the application.

Methods of the invention can be highly effective and amenable to automated, cost-effective high throughput assay that have application in a range of pharmaceuticals drug development programs. See the application at page 15, lines 25-30.

Of record in this case are two Rule 132 Declarations of Dr. Subroto Chatterjee, inventor on the present application and Professor at the Johns Hopkins University Medical School. Copies of Dr. Chatterjee's Declarations are attached.

Those Declarations detail, *inter alia*, particular difficulties that Dr. Chatterjee had to overcome to arrive at the present invention.

As mentioned above, the present case is a divisional case of parent application 08/774,104, now issued as U.S. Patent 5,919,687, copy thereof attached.

VI. ISSUES

The following issues are on appeal:

1. Whether claims 13 and 15-17 are unpatentable under 35 U.S.C. §112, second paragraph.

2. Whether claims 13 and 15-17 are unpatentable under 35 U.S.C. §112, first paragraph.

3. Whether claims 13-17 and 21 are unpatentable under 35 U.S.C. §103 over Chatterjee et al. (J. Biol. Chem., 1989), Ogita et al. (WO 9518119) and Ausubel et al. (Current Protocols in Molecular Biology).

VII. GROUPING OF THE CLAIMS

The rejected claims do ***not*** stand or fall together since each claim is considered separately patentable in its own right.

Appellant believes that all of the claims under appeal are separately patentable for the reasons set forth in the argument section which follows.

VIII. ARGUMENT

1. Rejection under 35 U.S.C. 112, second paragraph.

As indicated at page 2 of the Office Action, the grounds of the rejection are that the claim term "derivative" is indefinite.

Appellant disagrees. The term is specifically defined at page 8, lines 15-24 of the application. The required activity level of a "derivative" is further called for in independent claim 13.

Moreover, at page 8, line 25 through page 11, line 10 of the application further guidance is provided regarding what are suitable "derivatives".

Still further, at page 11, lines 5-10 of the application, it is disclosed that any particular material can be simply tested to determine if the material has appropriate activity to be a derivative.

Clearly, such extensive disclosure does not render the term indefinite.

At page 3 of the Final Office Action, it is indicated that amending independent claim 13 to recite structural relation to SEQ ID NO. 2 would overcome this rejection. However, Appellant does not consider such amendment required under 35 U.S.C. 112, second paragraph.

For such reasons, reversal of the final rejection under 35 U.S.C. 112, second paragraph is requested.

2. Rejection under 35 U.S.C. 112, first paragraph.

As grounds for the rejection, the following is stated at pages 3-4 of the Office Action:

> Claims 13 and 15-17 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences (modified by at least one deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2) that have not been disclosed in the specification. No description has been provided of the modified polypeptides encompassed by the claim.

Appellant strongly disagrees with such rejection.

Appellant's invention as recited in claims 13 and 15-17 is a method of identifying a compound useful in the treatment or diagnosis of a specific condition i.e., a human neutral sphingomyelinase (N-Smase) related disorder. Appellant does agree that the application is enabling for use of native enzyme in the method. However, Appellant cannot agree that the claims should recite only that enzyme and not other related N-Smases.

For example, and as the present application makes clear, practice of the invention is not limited to any particular N-Smase so long as it can provide acceptable function. See eg., pg. 15, lines 25-29 ; pg. 16, lines 4-15; and pg. 17, lines 8-10 of the present application (disclosing particular invention methods in which suitable enzyme fragments or derivatives are used).

Specific examples of such acceptable N-Smases are disclosed throughout the present application. For example, pg. 7, lines 19-26 and Figures 1 and 2 of the present application disclose physical characteristics of the preferred native enzyme. Additionally suitable enzyme fragments or derivatives provide good activity in the standard activity gel assays as discussed eg., at pg. 8, lines 16-23 of the present application. Preferred activity ranges in the assay have also been provided. Moreover, N-Smase fragments or derivatives with particular amino acid substitutions are disclosed at pg. 9, lines 1-20, for example. Nucleic acids that encode such suitable N-Smases are provided at pg. 10, lines 12-24 of the present application. Nucleic acids having preferred base pair sizes and N-Smases having desired functional domains are provided at pg. 10, line 12 to pg. 11, line 4 of the present application. Suitable enzyme isoforms are taught at

pg. 11, lines 21-25 of the present application.

As understood, the rejection takes the position that notwithstanding Appellant's disclosure of many specific N-Smases suitable for use with the claimed invention, use of anything but the native enzyme is not enabled on grounds that it would require undue experimentation to make and use the N-Smases. Appellant disagrees.

The present application provides examples of suitable N-Smases for use with the claimed invention including, but not limited to, the native enzyme. Should use of a particular enzyme fragment or derivative be needed in a specific invention embodiment, the specification provides more than ample guidance about selecting an appropriate fragment or derivative.

For example, preferred N-Smases including the native enzyme as well as fragments or derivatives thereof, exhibit good activity in the activity assay using ^{14}C-sphingomyelin and N-Smase peptide. See pg. 8, lines 16-23; and Example 6 of the present application.

Moreover, the chemical structure of the native N-Smase has disclosed both at the amino acid and nucleic acid levels. See Figures 1 and 2, for example. Important function domains in the structure are recognized. See pgs. 10-11 of the application, for example. Methods for producing suitable N-Smases, preferably by use of conventional recombinant means have been disclosed. See pg. 11, line 27 to pg. 12, line 10 of the application.

Accordingly, any testing needed to identify or confirm suitable N-Smases for use with the claimed invention is well within the level of experimentation permitted by the Federal Circuit. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Appellant disagrees with the rejection on other grounds.

For example, a worker in this field would be able to use the guidance provided by the instant disclosure to select appropriate N-Smases. Any inoperable embodiments of the type described by the rejection could be readily avoided. As stated by the CPPA:

> [M]any patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art.' ... There is nothing wrong with this so long as it would be obvious to one of skill in the art how to include these factors in such manner as to make the embodiment operative rather than inoperative. *In re Cook and Merigold*, 169 USPQ 299, 302 (C.C.P.A. 1971) (quoting *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

Thus, one of skill having read Appellant's disclosure would know to identify suitable N-Smases in addition to the native enzyme. Even if one assumes, *arguendo*, that a particular N-Smase fragment or derivative did not exhibit acceptable activity, that result, by itself, would not support the present enablement rejection. The worker would understand that another fragment or derivative as provided by the specification, could be tested and identified for suitable activity. The rejection has not provided any reason to doubt that the guidance provided by Appellant's disclosure could not be used to identify a range of acceptable N-Smases for use with the claimed methods.

It is noted that the rejection seems premised on the position that only claims drawn to exemplified invention embodiments satisfy the requirements of Section 112, first paragraph, notwithstanding the broader invention Appellant discloses.

Respectfully, such a position conflicts with established patent law. It is well-recognized that a patentee's invention is properly broader than specific embodiments identified in an application. Thus in *In re Anderson*, the CCPA reversed a rejection under Section 112, first paragraph and noted in particular (176 USPQ at 333):

> What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. **This it may not do**.... There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. (emphasis added).

Here, the claimed invention is broader than use of the native N-Smase singled-out in the rejection. As taught throughout Appellant's disclosure, the invention is compatible with a variety of suitable N-Smases including specified fragments and derivatives thereof.

Finally, it is noted that the Office has acknowledged the high level of knowledge in the art of enzymology. Final Office Action at pg. 8. Such knowledge is presumed to include information about N-Smase as well as acceptable fragments and derivatives of that enzyme.

For such reasons, reversal of the final rejection under 35 U.S.C. 112, first paragraph is requested.

3. Rejection under 35 U.S.C. 103.

As understood, the Final rejection maintains the position that it would be obvious to make the recombinant N-Smase enzyme of claim 13 by isolating the cited natural N-Smase enzyme, using that enzyme to obtain protein sequence and employing Ausubel's teachings to take that sequence, make cDNA, and then use that to obtain the recombinant N-Smase enzyme.

Appellant's disagree and submit that no *prima facie* case under Section 103 is presented by the cited documents, whether considered alone or in combination.

Among other things, no prior protein or nucleic acid sequence has been cited by the USPTO and knowledge of Ausubel's general cloning methods, without more, is not sufficient to render the claimed invention obvious.

This is particularly true in view of the Declaration of Dr. Subroto Chatterjee (dated November 12, 2002, copy attached) in which Dr. Chatterjee stated, among other things, that the USPTO position was not tenable with respect to the isolation of this particular enzyme. Specifically, he stated that it was not possible to make the recombinant N-Smase enzyme of claim 1 by using the approach outlined by the USPTO. Specifically, Dr. Chatterjee stated that it was not possible to obtain peptide sequence from the cited N-Smase enzyme and then use that sequence to make cloning probes. Declaration at ¶ 6-8.

However, and as stated by Dr. Chatterjee at ¶ 9-10 of the Declaration, he was able to make the recombinant N-Smase enzyme by using a protein expression cloning method. Use of that method according to Dr. Chatterjee required the isolation of a new antibody that was not taught or suggested from any of the cited references.

In the face of such compelling evidence that the recombinant N-Smase enzyme was indeed difficult to isolate and certainly not obvious from the cited references, the USPTO simply dismissed the evidence on grounds that Appellant should have been able to overcome his problems. Final Office Action at pgs. 9-10, bridging paragraph.

However, such a position clearly does not constitute basis for maintaining the instant rejection because it ignores actual technical difficulties Appellant and skilled colleagues (from Harvard University) faced when they attempted to isolate the recombinant enzyme. Declaration at ¶6-8. None of these difficulties or a solution to them is taught or suggested by the references as relied on.

Appellant notes that one alternative isolation method proposed by the Office at pg. 10 of the Action (expression cloning) would require use of an antibody that recognizes the N-Smase enzyme. None of the cited references provides any specific teaching or suggestion about how to obtain or make such an antibody. Not surprisingly, the Final Office Action is silent as to where

this antibody is to come from or whether a suitable antibody could be made at all. Indeed, it was the Appellant who discovered that it was possible to make a monospecific antibody against N-Smase and that the antibody could be used to isolate the recombinant enzyme. Declaration at ¶ 9-14.

At pages 11-12 of the Final Office Action, it is indicated that the obviousness rejection may be reconsidered if Applicant shows that the recombinant enzyme had unique properties which the natural enzyme of Chatterjee et al. does not. Although Appellant do not believe that such information is needed to address the instant rejection, it is provided below to help further prosecution.

In this regard, in the Supplemental Declaration of Dr. Subroto Chatterjee (of record, copy attached) Dr. Chatterjee states, among other things, that he had problems using the natural enzyme in the claimed method. Supplemental Declaration at ¶ 6. In particular, he states that the **natural enzyme had tightly associated proteases and phosphatases**. These unwanted proteins resist purification, degrade the natural enzyme, and render it unsuitable for use in the claimed method. Unlike the natural enzyme, the recombinant N-Smase was not found to be associated with any detectable protease or phosphatase activity. Supplemental Declaration at ¶ 7.

Dr. Chatterjee also states in the Supplemental Declaration that the **recombinant N-Smase enzyme was more stable then the natural enzyme**. Supplemental Declaration at ¶ 8. Specifically, he states that the recombinant enzyme was more stable then the natural enzyme which resulted in better assay sensitivity and reproducibility. Supplemental Declaration at ¶ 8.

As also stated in the Supplemental Declaration at ¶ 9, **storage of the natural N-Smase produced unwanted proteolytically digested products**. According to Dr. Chatterjee, such products can contribute to false or misleading identification of compounds in the claimed method. In contrast, storage of the recombinant N-Smase did not result in production of detectable digestion products. Supplemental Declaration at ¶ 9.

Accordingly, the natural N-Smase enzyme cited by the Office has characteristics that are different from the recombinant enzyme of Appellant's claim 13. For instance, and as the Supplemental Declaration makes clear, the recombinant enzyme does not have any detectable protease and phosphatase activity. In contrast, the natural enzyme has these damaging enzymes tightly associated with it. Moreover, the recombinant enzyme is more stable and less prone to proteolytic digestion when compared to the natural N-Smase enzyme. These and other advantages of the recombinant N-Smase enzyme make it especially useful for use in the claimed invention.

None of the cited references teach or suggest the foregoing problems associated with using the naturally-occurring N-Smase in accord with the claimed invention. Moreover, none of the cited references disclose or suggest Applicant's solution to these problems ie., making the recombinant N-Smase and using that enzyme instead of the natural enzyme in the claimed method.

Appellant's claim 14 also is separately patentable for the above-stated reasons and further because none of the cited documents disclose SEQ ID NO. 2 as recited in claim 14.

Appellant's claim 15 also is separately patentable for the above-stated reasons and further because none of the cited documents teach or suggest the features 1), 2) and 3) as recited in claim 15.

Appellant's claim 16 also is separately patentable for the above-stated reasons and further because none of the cited documents teach or suggest that the human neutral sphingomyelinase cleavage target is sphingomyelin as recited in claim 16.

Appellant's claim 17 also is separately patentable for the above-stated reasons and further because none of the cited documents teach or suggest that the human neutral sphingomyelinase

cleavage product is ceramide as recited in claim 17.

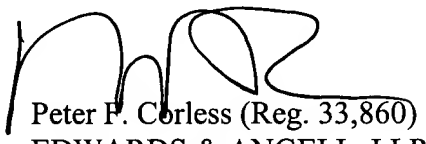
Appellant's claim 31 also is separately patentable for the above-stated reasons and further because none of the cited documents teach or suggest a fragment or derivative of the recombinant human neutral sphingomyelinase is at least about 70% identical to the protein of SEQ ID No. 2.

For such reasons, reversal of the final rejection under 35 U.S.C. 103 is requested.

SUMMARY

Therefore, for the foregoing reasons, it is respectfully requested that the Board reverse the Final Rejection in this application.

Respectfully submitted,



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APPENDIX

13. A method for identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder, comprising

contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof,

wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent, wherein the fragment or derivative of the human neutral sphingomyelinase has at least about 50% of the activity of the protein of SEQ ID No. 2.

14. The method of claim 13 wherein the human neutral sphingomyelinase has a sequence represented by SEQ ID NO:2.

15. The method of claim 13 wherein

1) a mixture is formed of I) a human neutral sphingomyelinase cleavage target, ii) the human neutral sphingomyelinase or fragment or derivative thereof, and iii) a candidate pharmacological agent;

2) the mixture is treated under conditions whereby, but for the present of the candidate agent, the human neutral sphingomyelinase of fragment or derivative cleaves the cleavage target to yield a cleavage product; and

3) the presence of the cleavage product is detected, wherein a reduced concentration of the cleavage product relative to a control mixture that does not contain the candidate agent identifies the candidate agent as a compound potentially useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder.

16. The method of claim 15 wherein the human neutral sphingomyelinase cleavage target is sphingomyelin.

17. The method of claim 15 wherein the human neutral sphingomyelinase cleavage product is ceramide.

31. The method of claim 13, wherein the fragment or derivative of the recombinant human neutral sphingomyelinase is at least about 70% identical to the protein of SEQ ID No. 2.

Docket No. 46906-DIV2 (71699)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	S. Chatterjee		
SERIAL NO.:	09/282,879	EXAMINER:	M. Rao
FILED:	March 31, 1999	GROUP:	1652
FOR:	RECOMBINANT N-SMASEs AND NUCLEIC ACIDS ENCODING SAME		

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

DECLARATION PURSUANT TO 37 CFR 1.132

The undersigned declares as follows:

1. I am the inventor of the above-identified application (hereafter the "subject application"). Additionally, I am a Professor of Pediatrics in the Department of Pediatrics at the Johns Hopkins University Medical School in Baltimore, MD.

2. As I understand it, the subject application discloses and claims, among other things, a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase (N-Smase) related disorder. A particular method includes contacting an agent with a recombinant N-Smase and analyzing enzyme activity in the presence and absence of the agent.

3. I have reviewed the Patent Office Action ("Office Action") dated April 9, 2002 issued in connection with the subject application. As I understand the Office Action, the patent Examiner rejected claims 13-17 as being obvious over Chatterjee et al. (*J. Biol. Chem.* (1989) 264: 12554); Ogita et al. (WO 95/18119); and Ausbel et al. (*Current Protocols in Molecular Biology*, J. Wiley & Sons (1987) pp. 10.0.3 -10.06). Hereinafter, the cited references are referred to as "Chatterjee", "Ogita" and "Ausbel",

respectively.

4. I am familiar with the contents of Chatterjee and Ausbel and I have read an English language translation of Ogita. As I understand it, Chatterjee reports isolation of naturally-occurring N-Smase from human urine, Ogita (as translated) reports isolation of a bacterial sphingomyelinase inhibitor from grass, and Ausbel discloses standard cloning methods.

5. I must respectfully disagree with the patent Examiner's position that the method I now claim is obvious over Chatterjee, Ogita and Ausbel. More specifically, I must disagree with the suggestion by the Examiner that it would be obvious to make the recombinant N-Smase featured in the claimed method.

6. For example, well before December 1996, I purified the N-Smase enzyme from human urine as described in Chatterjee. However, my attempt to obtain protein sequence information from the purified enzyme was not successful. Specifically, I found that the N-terminus of the N-Smase was blocked in a way that made it impossible to obtain useful protein sequence information using conventional methods.

7. Additionally, and well before December 1996, I contacted researchers at Harvard University (Cambridge, Mass) and asked them to obtain protein sequence information from the purified N-Smase enzyme at my direction. Using standard protein sequencing steps, they too were unable to obtain any useful protein sequence information from the purified enzyme.

8. I concluded that it was not possible to obtain useful protein sequence information from the purified N-Smase enzyme. I also concluded that it would not be possible to make the recombinant N-Smase by using approaches that required

peptide sequence information to make cloning probes.

9. I successfully made the recombinant N-Smase by using a protein expression cloning method.

10. In particular, and well before December 1996, I developed a monospecific antibody that bound the N-Smase enzyme. Preparation and use of that antibody was described in a research article I co-authored (Chatterjee, S. and N. Ghosh (1989) *J. Biol. Chem.* 21: 12554). The monospecific antibody I developed was not available to the public before December 1996.

11. I used the monospecific antibody to clone and isolate the recombinant human N-Smase featured in the claimed method. Particulars of the expression cloning approach I employed were provided in a research paper (Chatterjee, S et al. (1999) *J. Biol. Chem.* 24: 37407).

12. The expression cloning approach I used to clone and isolate the recombinant human N-Smase was not taught or suggested by Chatterjee, Ogita and Ausbel as cited by the Examiner.

13. In particular, there is no disclosure or suggestion in any of the cited references that it would be possible to make a monospecific antibody against human N-Smase and that the antibody could be used to clone and isolate the recombinant enzyme.

14. Additionally, there is no disclosure in any of the cited references that it would be impossible to clone and isolate the human N-Smase enzyme using standard protein sequencing techniques to make cloning probes.

15. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: NOV 12, 02

Subroto Chatterjee

Subroto Chatterjee

Doc. 316992

Docket No. 46906-DIV2 (71699)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	S. Chatterjee		
SERIAL NO.:	09/282,879	EXAMINER:	M. Rao
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THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

SUPPLEMENTAL DECLARATION PURSUANT TO 37 CFR 1.132

The undersigned declares as follows:

1. I am the inventor of the above-identified application (hereafter the "subject application"). Additionally, I am a Professor of Pediatrics in the Department of Pediatrics at the Johns Hopkins University Medical School in Baltimore, MD.

2. As I understand it, the subject application discloses and claims, among other things, a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase (N-Smase) related disorder. A particular method includes contacting an agent with a recombinant N-Smase and analyzing enzyme activity in the presence and absence of the agent.

3. I have reviewed the Patent Office Action ("Office Action") dated November 27, 2002 issued in connection with the subject application. As I understand the Office Action, the patent Examiner rejected claims 13-17 and 31 as being obvious over Chatterjee et al. (*J. Biol. Chem.* (1989) 264: 12554); Ogita et al. (WO 95/18119); and Ausbel et al. (*Current Protocols in Molecular Biology*, J. Wiley & Sons (1987) pp. 10.0.3

-10.06). Hereinafter, the cited references are referred to as "Chatterjee", "Ogita" and "Ausbel", respectively.

4. I am familiar with the contents of Chatterjee and Ausbel and I have read an English language translation of Ogita. As I understand it, Chatterjee reports isolation of naturally-occurring N-Smase from human urine, Ogita (as translated) reports isolation of a bacterial sphingomyelinase inhibitor from grass, and Ausbel discloses standard cloning methods.

5. I must respectfully disagree with the patent Examiner's position that the method I now claim is obvious over Chatterjee, Ogita and Ausbel. More specifically, I must disagree with the suggestion by the Examiner that it would be obvious to make the recombinant N-Smase featured in the claimed method.

6. For example, I have encountered substantial problems using the naturally-occurring N-Smase of Chatterjee et al. with the claimed method.

7. In particular, I found that even when the natural N-Smase enzyme is highly purified, it includes tightly associated proteases and phosphatases. Unfortunately, these enzymes degrade the enzyme. That activity renders the natural enzyme unsuitable for use with the claimed method. In contrast, the recombinant N-Smase of claim 1 is not associated with any detectable protease or phosphatase activity.

8. I also found that storage of the natural N-Smase enzyme, particularly long term, lowers its specific activity for substrate. This makes that natural enzyme unsuitable for use with the claimed method. Unlike that enzyme, the recombinant N-Smase of claim 1 is more stable. Use of the recombinant enzyme in the claimed method results in better sensitivity and reproducibility, for example.

9. In addition, storage of the natural N-Smase enzyme produces multiple proteolytically digested products. These products are not desirable for use with the claimed method. For example, one or more of the products can contribute to false or misleading identification of compounds according to the claimed method. In marked contrast, I have found that storage of the recombinant N-Smase of claim 1 does not result in detectable production of the digestion products.

10. As I understand the Chatterjee, Ogita and Ausbel references as cited by the Examiner, none of them disclose or suggest the foregoing problems of using the natural N-Smase enzyme with the claimed method.

11. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 28, 03

Subroto Chatterjee

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